value of a crossover index which is the ratio between a marker associated with the phase of calcification and a B1 marker associated with the phase of matrix maturation and the measured value of a marker associated with bone type I collagen.

REMARKS

Paper No. 4, the Official Action mailed June 1, 2001, has been carefully reviewed along with the cited and relied upon reference. Claims 1-17 remain in the application, and these claims define patentable subject matter warranting their allowance. Applicants accordingly request, with respect, favorable reconsideration and allowance.

Acknowledgement by the PTO of the receipt of applicants' papers filed under Section 119 is noted.

Claims 1-17 have been rejected under the second paragraph of Section 112. The rejection is respectfully traversed.

a. The PTO says the wording "... activity of osteoblasts ..." and "... action of osteoclasts" is vague and indefinite. Applicants strongly disagree. The present application is directed to those skilled in the present art. Moreover, those skilled in the art have applicants'

specification as guidance. It is clear to those skilled in the art, especially from Examples 1 to 3 and the statement appearing on page 16, lines 18-24, as to what activity or action is to be assessed.

Nevertheless, in deference to the examiner's views, to avoid unnecessary and excessive argumentation, and to even better particularly point out and distinctly claim the invention, claims 1 and 8 have been amended to add a relatively lengthy "whereby" clause. Applicants consider this clause to be explanatory and not to add any limitation which was not already previously present.

b. The PTO has held claim 1 to be vague and indefinite in its preamble as not being clear whether or not the tumor has metastasized from the bone to another organ or that the tumor has metastasized from an organ to the bone. Again, with respect, applicants strongly disagree.

It is clear to one skilled in the art from the specification of the present application that the tumor has metastasized not from the bone to another organ but from another body part to the bone. Thus, claim 1 is clear and definite for the recitation "A method of diagnosing bone metastasis of malignant tumor ...". The term "bone metastasis" means the metastasis of the tumor from another body part to the bone.

Nevertheless, to make the claim even more clear, the preamble has been amended slightly to recite "diagnosing metastasis of malignant tumor to bone ...".

c. The PTO has criticized claims 2, 6, 12 and 16 as being unclear with regard to the recited phases. Respectfully, applicants again disagree, and strongly state that the specification, directed to those skilled in the art, is clear. The claims which are to be read in light of the specification, are also clear; indeed, the claims are clear to those skilled in the present art even without reference to the specification.

The specification teaches in the second paragraph of page 3 that bone formation consists of three major phases, namely, the phase of osteoblast proliferation and matrix formation → the phase of matrix maturation → the phase of calcification. In addition, the specification provides cited prior art references. The aforementioned phases are concerned with the process of osteoblast differentiation/ maturation. However, the manner of **expression** (from a phenomenal point of view) is exactly the opposite.

Because osteoblasts change their function during differentiation and maturation, three phases occur during the process of bone formation. Therefore, the question of how many phases there are of osteoblast proliferation is not an

appropriate or meaningful question, and framing a question in terms of whether a certain number of phases of osteoblast proliferation exist is inaccurate. The fact is that there are three phases in the process of bone formation which take place in connection with osteoblast differentiation/ maturation. The three phases are (1) the phase of osteoblast proliferation and matrix formation → (2) the phase of matrix maturation → (3) the phase of calcification.

The Examiner also asks whether the marker is associated with only one particular phase. The marker is not precisely and clearly associated with only one particular phase. The fact is that PICP and PINP, BALP, and osteocalcin are notably produced mainly during the phase of matrix maturation, and the phase of calcification, respectively.

Further, the Examiner states that the claims suggest that there are several phases pf osteoblast proliferation, calcification and matrix maturation. As mentioned above, osteoblasts change their function during differentiation and maturation. The process of osteoblast differentiation/maturation is as follows: mesenchymal precursor cell → preosteoblast → osteoblast.

Claims 2, 6, 12 and 16 are based on the above facts, and would be readily understandable to those skilled in the present art to whom the present specification is

directed. Claims 2, 6, 12 and 16 are clear, definite and in full compliance with the second paragraph of 35 U.S.C. 112.

d. The examiner has suggested elimination of the acronyms or abbreviations, and this has been done above.

e. The PTO has criticized the expression "crossover index" in claims 6, 7, 16 and 17. Applicants believe that because of applicants' use of the term "or" following the term "crossover index", claims 6 and 16 have been misunderstood. Accordingly, claims 6 and 16 have been appropriately amended to make them more clear.

In claim 6, each of the portions following the previously used word "or" is a definition of "crossover index". The word "or" means "namely". The same is true for claim 16. Claim 7 is dependent on claim 6. It is therefore clear that "a crossover index between osteocalcin and PICP or PINP" and "a crossover index between osteocalcin and BALP" mean " a crossover index or the ratio between osteocalcin and PICP or PINP" and "a crossover index or he ratio between osteocalcin and BALP", respectively. The same is applied to claim 17.

In the present specification, "the value of a crossover index" is used to mean a value obtained by dividing one of two measure values by the other. Since "the value of crossover index" is used in claims 6, 7, 16 and 17 by

defining the meaning thereof in claims 6 and 16, these claims are neither vague not indefinite.

From the explanation above, it will be clear that the amendments introduced into claims 6 and 16 do not add any limitations to these claims. Indeed, for the most part, all of the amendments presented above are of a formal nature only, made to place the claims in better form consistent with U.S. practice. Applicants do not see that such amendments are "narrowing" because the scope of the claims has not been reduced and the meaning of the claims has not changed. Thus, in these regards, no limitations have been added and none are intended.

Applicants respectfully repeat that the claims are clear and readily understood by those skilled in the art, particularly after reading applicants' specification. This is all that is required. Applicants request withdrawal of the rejection under Section 112.

Claims 1-5 have been rejected as anticipated under Section 102 by Plebani et al (hereinafter "Plebani"). This rejection is respectfully traversed.

Plebani provides information obtained by comparing and discussing the sensitivity and specificity of serum markers, such as a marker of bone formation and a marker of bone resorption, regarding each marker when each of the

markers was solely used by itself for the detection of bone metastases. In contrast, the present invention is characterized by the combined use of a marker that reflects the activity of osteoblasts and a marker that reflects the action of osteoclasts, in the diagnosis of bone metastases. Plebani neither discloses nor suggests the combined use of markers in accordance with the present invention. Therefore, claims 1-5 are not anticipated by Plebani.

It should be noted that claim 1 recites a method of using a first "marker that reflects the activity of osteoplasts and a [second] marker that reflects the action of osteoclasts". This is clearly a combined use, and applicants do not see how Plebani can possibly be interpreted as disclosing such a combined use. Nevertheless, so as to bring out this point more clearly, claim 1 has been amended to add the word "both" in line 2 thereof before the word "using". Again, applicants consider such an amendment to be "cosmetic", i.e. of a formal nature only made to place claim 1 in better form. Such an amendment is not "narrowing" because the scope of claim 1 has not been reduced and the meaning of claim 1 has not changed by such an amendment. No limitation has been added in this regard and none is intended.

Applicants respectfully request withdrawal of the rejection based on Section 102.

Applicants note that claims 6-17 have not been rejected on the basis of any prior art. Applicants accordingly understand that such claims are deemed by the PTO to define novel and unobvious subject matter under Sections 102 and 103.

Favorable consideration and early formal allowance are respectfully urged.

Respectfully submitted,

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Version with Markings to Show Changes Made

Scope has no changed

1. (Amended) A method of diagnosing ~~bone~~ metastasis of malignant tumor to bone using both a marker that reflects the activity of osteoblasts and a marker that reflects the action of osteoclasts, whereby the amelioration of bone metastasis or therapeutic effect and the degree of the exacerbation of bone metastasis are diagnosed correctly by monitoring said two markers, one associated with osteoblasts and targeted to evaluation of therapeutic effect, and the other associated with osteoclasts and targeted to evaluation of worsening of the disease.

8. (Amended) A method of evaluating the therapeutic efficacy of a drug using a marker that reflects the activity of osteoblasts and a marker that reflects the action of osteoclasts, whereby the amelioration of bone metastasis or therapeutic effect and the degree of the exacerbation of bone metastasis are diagnosed correctly by monitoring said two markers, one associated with osteoblasts and targeted to evaluation of therapeutic effect, and the other associated with osteoclasts and targeted to evaluation of worsening of the disease.

3. (Amended) The method according to claim 1, wherein the marker that reflects the activity of osteoblasts is:

(1) ~~PICP~~ Carboxyterminal propeptide of type I procollagen or ~~PINP~~ Amino terminal propeptide of type I procollagen and osteocalcin; or

(2) ~~BALP~~ Bone specific alkaliphosphatase and osteocalcin.

5. (Amended) The method according to claim 1, wherein the marker that reflects the action of osteoclasts is deoxypyridinoline and/or ~~ICTP~~ Carboxyterminal telopeptide of type I collagen.

7. (Amended) The method according to claim 6, which is based on the value of a crossover index between osteocalcin and ~~PICP~~ Carboxyterminal propeptide of type I procollagen or ~~PINP~~ Amino terminal propeptide of type I procollagen and the measured value of ~~ICTP~~ Carboxyterminal telopeptide of type I collagen, or on the value of a crossover index between osteocalcin and ~~BALP~~ Bone specific alkaliphosphatase and the measured value of ~~ICTP~~ Carboxyterminal telopeptide of type I collagen.

13. (Amended) The method according to claim 8, wherein the marker that reflects the activity of osteoblasts is:

(1) ~~PICP~~ Carboxyterminal propeptide of type I procollagen or ~~PINP~~ Amino terminal propeptide of type I procollagen and osteocalcin; or

(2) ~~BALP~~ Bone specific alkaliphosphatase and osteocalcin.

15. (Amended) The method according to claim 8, wherein the marker that reflects the action of osteoclasts is deoxypyridinoline and/or ~~ICTP~~ Carboxyterminal telopeptide of type I collagen.

17. (Amended) The method according to claim 16, which is based on the value of a crossover index between osteocalcin and ~~PICP~~ Carboxyterminal propeptide of type I procollagen or ~~PINP~~ Amino terminal propeptide of type I procollagen and the measured value of ~~ICTP~~ Carboxyterminal telopeptide of type I collagen, or on the value of a crossover index between osteocalcin and ~~BALP~~ Bone specific alkaliphosphatase and the measured value of ~~ICTP~~ Carboxyterminal telopeptide of type I collagen.

6. (Amended) The method according to claim 1, ~~which is~~ based on the value of a crossover index ~~or~~ which is the ratio between a marker associated with the phase of calcification and a marker associated with the phase of osteoblast proliferation and matrix formation and the measured value of the marker that reflects the action of

osteoclasts, or on the value of a crossover index ~~or~~ which is the ratio between a marker associated with the phase of calcification and a marker associated with the phase of matrix maturation and the measured value of a marker associated with bone type I collagen.

16. (Amended) The method according to claim 8, ~~which is~~ based on the value of a crossover index ~~or~~ which is the ratio between a marker associated with the phase of calcification and a marker associated with the phase of osteoblast proliferation and matrix formation and the measured value of the marker that reflects the action of osteoblasts, or on the value of a crossover index ~~or~~ which is the ratio between a marker associated with the phase of calcification and a marker associated with the phase of matrix maturation and the measured value of a marker associated with bone type I collagen.